高 雄 榮 民 總 醫 院
白血病診療原則

2018年02月22日 第一版

兒童癌症醫療團隊擬訂

注意事項：這個診療原則主要作為醫師和其他保健專家診療癌症病人參考之用。假如你是一個癌症病人，直接引用這個診療原則並不恰當，只有你的醫師才能決定給你最恰當的治療。

修訂指引

- 本共識依下列參考資料制定版本
  - 台灣兒童癌症研究群(TPOG)，TPOG_ALL_2013_Revised_6.30.2017

會議討論

上次會議：NA

本共識與上一版的差異

上一版	新版
1.無。	1.2018年將癌症收案對象兒童(<18歲)區分出來，故新制定兒童癌症-白血病診療指引。

兒癌-Leukemia

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臨床診療指引　2018年第一版

◎評估

-病史、理學檢查
-營養及日常體能狀態
-胸部X光
-血液常規
-電解質及肝腎功能
-腹部超音波
-心臟超音波
-骨髓穿刺及血液抹片檢查

兒癌-Leukemia AML

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◎兒童癌症常見白血病:

-Acute myeloid leukemia(AML, 急性骨髓性白血病)

◎Diagnostic tool:

-Peripheral blood smear

-Bone marrow aspiration and pathology

-Cytogenetic and gene mutation test

-flowcytometry

◎Classification:

The initial diagnosis of AML, including the subtyping, was established according to the French-American-British (FAB) classification and the results of cytochemistry and immunological studies. Diagnosis of the M0 and M7 subtypes was confirmed by immunologic methods. The karyotypes were interpreted according to the International System for Human Cytogenetics Nomenclature. Common fusion transcripts were detected by reverse transcriptase (RT) PCR assays followed by Southern blot analysis. The diagnosis and classification of each case were also evaluated according to the new classification system of the World Health Organization

◎Treatment:

The TPOG-AML-2008 protocol consisted of 2-3 courses induction therapy, 4 courses consolidation therapy and 2 course of intensification and maintenance therapy.

- **Induction phase**
- **Consolidation phase (Post-remission 1)**
- **Intensification & phase Maintenance (Post-remission 2)**

- **Hematopoietic stem cell transplantation**
- **Supportive care**

兒癌– Leukemia AML

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◎A: Induction phase

A-1 Induction 1 IA 3+8 regimen (at least 3 weeks)

I: Idarubicin 9mg/m^2/q.o.d IV.×3 day 1, 3, 5

A: Ara-C 100mg/m^2/ day Civd×8 day 1-8

TIT: day 1

Rest from day 9 to day 21 or until hemogram recovery (PL.>100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

Note. 1. If a remission could not be induced after induction 1, the patient will be assigned into induction 2

2. If the patient achieved remission after induction 1 will be assigned to enter induction 3 (A-3) directly.

3. TIT performed under the followings

Age(yrs)	MTX(mg)	Ara-C(mg)	Hydrocortisone(mg)	Volume(ml)
<1	6	6	6	8
1-2	8	20	8	8
2-3	10	25	10	10
3-9	12	30	12	12
>9	15	30	15	12

Note: The drugs used in TIT should be given mixed together.

兒癌– Leukemia AML

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◎ A:Induction phase

A-2 Induction 2　IAE 3+8+5 regimen (at least 3 weeks)

I:	Idarubicin	9mg/m^2/q.o.d×3	day 1, 3, 5
A:	Ara-C	100mg/m^2/ day Civd×8	day 1-8
E:	Etoposide	100mg/m^2/d　> 1 h ivD in 0.9% saline x 5	day 1-5
TIT:			day 1

Rest from day 9 to day 21 or until hemogram recovery (PL.>100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

Notes: Proceed to A-3 regimen no matter complete remission achieved or not

兒癌– Leukemia AML

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◎ A:Induction phase

A-3 Induction 3　Mit.A 4+8 regimen (at least 3 weeks)

Mit:	Mitoxantrone	8mg/m^2/qd. >1hr.ivD.×4	day 2, 3, 4,5
A:	Ara-C	100mg/m^2/ day Civd×8	day 1-8
TIT:			day 1

Rest from day 9 to day 21 or until hemogram recovery (PL.>100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

Notes: 1.If the patient still has not achieved CR induction failure confirmed.

2. Proceed to B regimen no matter complete remission achieved or not

兒癌– Leukemia AML

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◎ B:Consolidation phase (Post-remission 1)

Note:Criteria for start of each cycle of consolidation especially with Hi-A:PL.>10x103/mm3 and ANC >1000/mm3.

B-1 HiA-E. (at least 3 weeks)

Hi-A: High-dose Ara-C 1g/m^2/q 12 h, 2-3 hr ivD x 10 day1-5

E: Etoposide 100mg/m^2/d 1-2 h ivD in 0.9% saline

after Ara-C x 5 day 1-5

TIT: day 1

Rest from day 6 to day 21 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

B-2 CAE (at least 2 weeks)

C: Cyclophosphamide 200mg//m^2/qd, 2-3 hr ivD x 5 day1-5

A: Ara-C 100mg/m^2/ day Civdx5 day 1-5

E: Etoposide 100mg/m^2/d > 1 h ivD in 0.9% saline x 5 day 1-5

TIT: day 1

Rest from day 6 to day 14 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

兒癌– Leukemia AML

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臨床診療指引　2018年第一版

◎ B:Consolidation phase (Post-remission 1)

Note:Criteria for start of each cycle of consolidation especially with Hi-A:PL.>10x103/mm3 and ANC >1000/mm3.

B-3 HiA- Mit. (at least 3 weeks)

Hi-A: High dose Ara-C 1g/m^2/q 12 h, 2-3 hr ivD x 10 day1-5

Mid: Mitoxantrone 8mg/m^2/ ivD ihr.

after Ara-C x 4 day2-5

TIT: day 1

Rest from day 6 to day 21 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

B-4 CAE (at least 2 weeks)

C: Cyclophosphamide 200mg//m^2/qd, 2-3 hr ivD x 5 day1-5

A: Ara-C 100mg/m^2/ day Civdx5 day 1-5

E: Etoposide 100mg/m^2/d > 1 h ivD in 0.9% saline x 5 day 1-5

TIT: day 1

Rest from day 6 to day 14 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).
Bone marrow examination (BM) before next course

◎C: Intensification & phase Maintenance (Post-remission 2)

C-1a: IA 3+7 regimen (at least 3 weeks)

I:	Idarubicin	9mg/m^2/q.o.d×3	day 1, 3, 5
A:	Ara-C	100mg/m^2 /day Civd. ×7	day 1-7
TIT:			day 1

Rest from day 8 to day 21 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).

C-1b: CAE (at least 2 weeks)

C:	Cyclophosphamide 200mg//m^2/qd, 2-3 hr ivD x 5		day1-5
A:	Ara-C	100mg/m^2/ day Civd×5	day 1-5
E:	Etoposide	100mg/m^2/d > 1 h ivD in 0.9% saline x 5	day 1-5
TIT:			day 1

Rest from day 6 to day 14 or until hemogram recovery (PL. >100x10^3/mm^3 and ANC >1000/mm^3).

兒癌– Leukemia AML

高雄榮民總醫院
臨床診療指引　2018年第一版

◎C: Intensification & phase Maintenance (Post-remission 2)

C-1c: Maintenance (3Weeks)

MTX 20-30mg/ m^2/wk IM/or PO	week 1,2,3
6-MP 75mg/ m^2/day PO	day 1-21

C-2:

Repeat C-1(a+b+c) regimens one cycle (8 weeks)

Bone marrow examination at the end of C1 and C2

Note: The total cumulative dose of Idarubicin, Mitoxantrone and Etoposide will be 81~108mg/m^2, 64mg/m^2, and 3000mg/m^2 respectively. The total equivalent dose of Idarubicin and Mitoxantrone to Doxorubicin will be around (154~205) +320=474~525 mg. Doxorubicin or 249~276 mg Idarubicin.

◎ C: Intensification & phase Maintenance (Post-remission 2)

C-2: repeat courseC1a+1b+1c regimen one cycle (8 weeks)

*Special note for whole protocol: Be check CBC+DC & BM every next course & C-2 day 57

Note:1. The total cumulative dose of Idarubicin, Mitoxantrone and Etoposide will be 81~108mg/m^2, 64mg/m^2, and 3000mg/m^2 respectively. The total equivalent dose of Idarubicin and Mitoxantrone to Doxorubicin will be around (154~205) +320=474~525 mg. Doxorubicin or 249~276 mg Idarubicin.

2. GCF, Allopurinol, trimethoprim-sulfamethoxazole will be used under the guideline mentioned above

3. CNS prophylaxis will be performed as the following under the guideline:

Age(yrs)	MTX(mg)	Ara-C(mg)	Hydrocortisone(mg)	Volume(ml)
<1	6	6	6	8
1-2	8	20	8	8
2-3	10	25	10	10
3-9	12	30	12	12
>9	15	30	15	12

兒癌- Leukemia AML

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Hematopoietic stem cell transplantation

Hematopoietic stem cell transplantation, including allogeneic bone marrow/or peripheral blood stem cell transplantation, cord-blood transplantation, autologous bone marrow/or peripheral blood stem cell transplantation, when feasible, can be performed individualized after 2nd course consolidation phase completed under the judgment of physician.

◎ Supportive care

Granulocyte-colony stimulating factor (G-CSF, 200 μ g/m^2/day or 5-10 μ g/kg/day SC) can be administered each day during marrow aplasia induced by induction, consolidation, or intensification chemotherapy and prophylactically over 36 to 48 hours after the end of each HDAra-C-containing course. Bactrim (trimethoprim-sulfamethoxazole) for prophylaxis of *Pneumocystis carinii* pneumonitis was given 3 days a week beginning at 2 weeks after the initiation of induction therapy and continuing to 6 months after the completion of chemotherapy.

兒癌- Leukemia AML

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臨床診療指引　2018年第一版

◎ Note for general

1. **Stem cells transplantation** can be considered individualized after B-1&2 post-remission1 therapy completed
2. **G-CSF** should be used if the WBC count <1000/ mm^3 or ANC <500/mm^3 or prophylactically for the next chemotherapy having experience with neutropenia over 3 days in the previous therapy.
3. **CNS disease prophylaxis and treatment**

   3-1.CNS prophylaxis should be performed on 1st day of each cycle of all phase treatment and the CSF should be examined for CNS disease.

   3-2. TIT performed under the followings

Age(yrs)	MTX(mg)	Ara-C(mg)	Hydrocortisone(mg)	Volume(ml)
<1	6	6	6	8
1-2	8	20	8	8
2-3	10	25	10	10
3-9	12	30	12	12
>9	15	30	15	12

Note: The drugs used in TIT should be given mixed together.

兒癌– Leukemia AML

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臨床診療指引　2018年第一版

◎ Note for general

3-3. If the **CNS disease** is present at diagnosis (defined by the presence of more than $5x10^6$/l leukemic blasts in CSF cyto-spin preparation or any blast found in CSF smear) children should receive two courses of TIT each week until the CSF is clear plus two further courses.

4. **Allopurinol** should be given as soon as possible after diagnosis at a dose of 5 mg/kg
5. For the children less than 12 ms old the dosage of drugs used in induction, consolidation and intensification should be reduced by 25%.
6. If the patients have failed to achieve complete remission after 3 courses induction that is considered treatment failure. They can try to proceed to consolidation therapy or to enter another treatment modality.

兒癌– Leukemia AML

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臨床診療指引　2018年第一版

◎ Note for general

7. If the hemogram of patients near recovery stage, but the rest period for waiting recovery is longer than 4 week, their following treatment could be start under components treatment and necessary support therapy.
8. Because of fever, diarrhea, conjunctivitis, cerebellar ataxia etc. are common **side effects of high dose Ara-C treatment**, the following therapy should be given at least 4 days:
   a. IV fluid (eg. 0.33% G/S) 2000ml / m^2/day
   b. Dexamethasone 20mg/ m^2/day divided into 2-4 doses IV
   c. Acetaminophen 40mg/kg/day divided into 4 PO
9. Try the best to perform cytogenetic/and or molecular genetic study needed.

兒癌- Leukemia ALL

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臨床診療指引　2018年第一版

◎兒童常見白血病:

-Acute lymphoid leukemia(ALL, 急性淋巴性白血病)

◎Diagnostic tool:

-Peripheral blood smear
-Bone marrow aspiration and pathology
-Cytogenetic and gene mutation test
-flowcytometry

兒癌－Leukemia ALL

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◎RISK CLASSIFICATION

Patients are classified into one of three categories (standard-, high-, or very high-risk) based on the presenting age, leukocyte count, presence or absence of CNS-3 status or testicular leukemia, immunophenotype, cytogenetics and molecular genetics, DNA index, and early response to therapy. Hence, definitive risk assignment will be made after completion of remission induction therapy. The criteria and the estimated proportion of patients in each category are provided below.

◎ CRITERIA FOR STANDARD RISK ALL

(1).B-lymphoblastic ALL with DNA index ≥ 1.16 [or hyperdiploidy (51-68)], *TEL-AML*1 fusion, or age 1 to 9.9 years and presenting WBC < 50,000/mm^3. AND

(2).Must not have:

-CNS 3 status (≥ 5 WBC/μL of cerebrospinal fluid with morphologically identifiable blasts or cranial nerve palsy).

-Overt testicular leukemia (evidenced by ultrasonogram).

-Adverse genetic features: t(9;22) or *BCR-ABL1* fusion; t(1;19) with *E2A-PBX1* fusion; rearranged *MLL* (as measured by FISH and/or PCR); or hypodiploidy (< 44 chromosomes).

-Poor early response (≥ 1% lymphoblasts on day 15 of remission induction, ≥ 0.01% lymphoblasts by immunologic or molecular methods on remission date).

兒癌– Leukemia ALL

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◎ CRITERIA FOR HIGH-RISK ALL

All cases of T-cell ALL and those of B- lymphoblastic ALL that do not meet the criteria for standard-risk or very high-risk ALL.

◎ CRITERIA FOR VERY HIGH-RISK ALL

(1).t(9;22) or *BCR-ABL1* fusion (with MRD ≥0.01% after remission induction including dasatinib (60 mg/m^2 per day).
(2).Infants with t(4;11) or *MLL* fusion.
(3).Induction failure or ≥1% leukemic lymphoblasts in the bone marrow on remission date (with the exception of hyperdiploid (51-68) and *TEL-AML1* cases who should have positive MRD after consolidation therapy).
(4).≥0.1% leukemic lymphoblasts in the bone marrow in week 7 of continuation treatment (i.e. before reinduction I, ~14 weeks post remission induction).
(5).Re-emergence of leukemic lymphoblasts by MRD (at any level) in patients previously MRD negative.
(6).Persistently detectable MRD at lower levels.
(7).Early T-cell precursor (ETP) ALL, defined by lack of expression of CD1a and CD8 and low or absent expression of CD5 together with aberrant expression of myeloid and hematopoietic stem cell markers (such as CD13, CD33, CD34 and CD117).

兒癌－Leukemia ALL

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◎ Treatment Plans

4.1 Induction (6-7 weeks)

Induction treatment will begin with prednisone, vincristine, epirubicin, L-asparaginase and triple intrathecal treatment, followed by cyclophosphamide plus cytarabine plus mercaptopurine. Epirubicin may be delayed in patients with febrile neutropenia, evidence of mucositis or increased hyperbilirubinemia (i.e., total bilirubin ≥ 2.0 mg/dl and direct bilirubin > 1.4 mg/dl). Patients with mucositis should be evaluated for herpes simplex infection and treated with acyclovir if work-up is positive.

It is a good practice to give steroids in patients with large leukemic burden (WBC>100,000;large organs especially mediastinum) to reduce the risk of massive tumor lysis syndrome. The use of steroids is limited to 1-3 days.However, for our MRD-oriented protocol, earlier use of steroids before combination chemotherapy could, on the other hand, not be used.

兒癌– Leukemia ALL

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◎ Treatment Plans

Drug	Dosages and Routes	Doses	Schedule (Day)
Prednisolone ‡	40 mg/m^2/d P0 (tid)	84	1-28 (28 days) Tapering in 1 week
Dexamethasone (for ETP immunophenotype)	10 mg/m^2/day PO (divided t.i.d.)	63	Days 1-21
	4 mg/m^2/day PO (divided t.i.d)	9	Days 22-24
	2 mg/m^2/day PO(divided t.i.d)	12	Days 25-28
Zantac (only for induction; may not be given in infant ALL)			
Vincristine	1.5 mg/m^2 (maximum 2 mg)	4	1, 8, 15, 22
Epirubicin	20 mg/m^2	2	1, 8*
L-asparaginase	6,000 U/m^2 IM **	6	3, 5, 7, 10, 12, 14
TIT	The first TIT is at the disappearance of blast from PB, no later than Day 10. Subsequent TITs depend on CSF finding and risk group.		

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◎ Treatment Plans

Further treatment is based on the result of MRD on day 15

Drug	Dosages and Routes	Doses	Schedule (Day)
If Day 15, MRD < 1%			
L-asparaginase		3	17, 19, 21
If Day 15, MRD ≥ 1% and < 5%			
L-asparaginase		6	17, 19, 21, 24, 26, 28
Cyclophosphamide	1000mg/m^2 IV 6 hrs	1	22†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m^2/dose	14	Days 22-35†
Dasatinib (*Ph*+)§	60mg/m^2/day	Daily	Starting Day 15 of induction to continue until end of treatment
If Day 15, MRD ≥ 5%			
L-asparaginase		6	17, 19, 21, 24, 26, 28
Cyclophosphamide	300mg/m^2 IV 1 hr	4	q12 hrs on Days 22-23†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m^2/dose	14	Days 22-35†
Dasatinib (*Ph*+)§	60mg/m^2	Daily	Starting Day 15 of induction to continue until end of treatment

兒癌– Leukemia ALL

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◎ Treatment Plans

Exception !!

All T-cell ALL patients who have MRD (on day 15)　0-- < 5 % need adding

Cyclophosphamide	1000mg/m^2 IV 6 hrs	1	22†
Cytarabine	75mg/m^2/dose IV 30 mins	8	Days 23-26, 30-33†
6-mercaptopurine	60mg/m2/dose	14	Days 22-35†
L-asparaginase		6	17, 19, 21,24,26,28

* Day 8 dose may not be given or be delayed in apparent standard-risk patients with clearance of blasts and leukopenia.

** No special concern of risk of bleeding; IM irrespective of platelet count.

§ May be given to cases with other genetic abnormalities such as *EBF1-PDGFRB* or *NUP214-ABL1* (BCR-ABL1-like ALL)

‡ Oral prednisone can be substituted with methylprednisolone at 40 mg/m2/day IV (t.i.d.) for

◎ Treatment Plans

patients who cannot tolerate the oral medication

†May be delayed for 3 to 7 days if Day 22 WBC<1000 and Day 22 APC<300 and the last few doses of cytarabine and 6-mercaptopurine may be omitted if the patient develops infection with leukopenia and/or neutropenia.

-To avoid dry tap of bone marrow aspiration on day 1 and day 15, No. 16 of BMA needle is recommend.

For infant with *MLL+*

Agent	Dosage and Route	Doses	Schedule
Clofarabine	25 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 22-26
Cyclophosphamide	300 mg/m^2/day, 1-hour IV infusion	5	Days 22-26

Day 22 Vincristine will be omitted for infants with MLL+

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

a. No dose modifications are planned for prednisolone, asparaginase, or epirubicin therapies during induction. Only acute hemorrhagic pancreatitis or severe coagulopathy resulting in stroke syndrome warrants discontinuation of asparaginase. In the case of mild hypersensitivity reactions (e.g., facial flushing or urticaria) to asparaginase, patients will be premedicated with diphenhydramine before the next dose. If the hypersensitivity reactions recur or there is an anaphylactic reaction, patients may switch to the Erwinia preparation (at 20,000 U/m^2 three times a week). If it is not possible to obtain Erwinia-asparaginase, no further asparaginase treatment will be administered.

b. Dose Adjustment for infants: With the exception of vincristine and prednisolone, all dosages given to infants (< 1 year) will be based on body surface area. 2/3, 3/4, 4/4 dose based on body surface will be given for age <6, 6-12, and >12 months, respectively (As TPOG-ALL-2002 protocol). For infants < 1 month of age, or for infants < 3 months of age born significantly prematurely, a 50% reduction in dosages of clofarabine, epirubicin, asparaginase, etoposide, methotrexate, mercaptopurine, cyclophosphamide, and cytarabine should be made.The vincristine dosage for patients < 12 months of age or < 10 kg weight is 0.05 mg/kg/dose. Since the dose of prednisolone in TPOG-ALL-2013 is only 40 mg/m^2/day, the dose will based on body surface without reduction.

◎ Treatment Plans

c. Mild vincristine toxicity (jaw pain, constipation, decreased deep tendon reflexes) is anticipated. Only stroke-like syndrome or a motor paralysis warrants discontinuation of this drug. If persistent, severe abdominal cramps or gait impairment develop, the dose will be reduced to 1 mg/m^2. The use of azole compound (such as fluconazole, itraconazole, voriconazole), azithromycin or erythromycin may increase the toxicities of vincristine by inhibiting cytochrome P450; these drugs should be stopped one day or more before vincristine treatment.

d. On day 1, epirubicin may be delayed in patients with total bilirubin ≥ 2.0 mg/dl and direct bilirubin > 1.4 mg/dl. Omit this dose of epirubicin if total bilirubin is still ≥ 2 mg/dl and direct bilirubin > 1.4 mg/dl on day 8. Epirubicin may be given as soon as hyperbilirubinemia has resolved. The second dose of epirubicin on day 8 may be delayed in standard-risk patient who has cleared circulating blasts and has severe neutropenia, or in any risk group patient who is sick with infection. The second dose of epirubicin may be omitted in standard-risk patient if needed.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

e. Trimethoprim (150 mg/m^2/day) plus sulfamethoxazole (750 mg/m^2/day) (TMP-SMZ) to prevent Pneumocystis carinii pneumonia will be given to all patients daily in two divided doses starting on day 15, if prophylactic antibiotics are not given. After CR is achieved, TMP-SMZ will be given on Monday, Wednesday and Friday until 1 month after cessation of treatment. Adverse reactions to TMP-SMZ: For patients with rash, neutropenia, fever and other reactions presumed due to TMP-SMZ, withhold drug until reaction resolved. Do not re-challenge patients with severe exfoliative dermatitis (Stevens-Johnson syndrome), anaphylaxis or urticaria. If adverse reaction recurs, change Pneumocystis carinii pneumonia prophylaxis to pentamidine (preferable), or atovaquone.

f. Bone Marrow Evaluations

Day 15 (or between D15 and day 19 if bone marrow procedure can not be performed on holiday) A bone marrow aspirate will be done on day 15 of remission induction to assess antileukemic response. The presence of ≥ 1% of leukemic blasts in the bone marrow by morphologic exam or by MRD study is an indication for 3 additional doses of L-asparaginase to be administered between days 24 and 28

Patients with the presence of ≥ 1% leukemic blasts in the bone marrow on day 15 receive cyclophosphamide, mercaptupurine, and cytarabine as scheduled if their clinical condition permits, regardless of their ANC. For other patients, the treatment may be delayed for 3 to 7 days to allow some degree of hematopoietic recovery if APC (ANC + monocyte) < 300/mm^3.

◎ Treatment Plans

End of Induction-MRD response

A bone marrow aspirate will be performed on day 38-42 of remission induction, depending on when ANC has recovered to > 300/mm^3, WBC to > 1,000/mm^3, and platelet count to > 50,000/ mm^3. If the date falls on a week-end or holiday, the procedure may be performed on closest working day. MRD level will be determined in this bone marrow sample. Poor response will be defined as MRD level ≥ 0.01% (one or more lymphoblasts among 10^4 bone marrow mononuclear cells) by either immunologic or molecular assay. If the result of MRD is positive, provisional standard-risk cases will then be re-classified as high-risk (MRD ≥ 0.01% but less than 1%) or very high-risk (MRD ≥ 1%), and will receive subsequent 3 doses of HDMTX at a higher dosage (i.e., 5 gm/m^2). (These patients would have received the first HDMTX of consolidation therapy at 2.5 gm/m^2.)

◎ Treatment Plans

g. Transfusion Guidelines

A). Bleeding is generally not a problem during induction treatment (after asparaginase treatment); therefore platelet transfusion is usually not necessary in them even though they may have thrombocytopenia, unless there is fever or mucositis.

B). There is no need to measure coagulation status during remission induction (after asparaginase treatment) because coagulopathy is expected. Unless there is bleeding complication, fibrinogen preparation or cryoprecipitate should be avoided because they can enhance the risk of thrombosis caused by asparaginase and prednisone. Note that fresh frozen plasma can supply asparagine to leukemic cells and should also be avoided.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

4.2 IT Chemotherapy During Induction Treatment

As a traumatic lumbar puncture at diagnosis may result in a poorer outcome and the need for extra intrathecal therapy subsequently, all diagnostic lumbar punctures will be performed by experienced personnel, preferably under general anesthesia or deep sedation. Triple intrathecal chemotherapy (MHA) will be administered immediately after cerebrospinal fluid is collected at the disappearance of blast from PB, no later than D10. The dosage is age-dependent as following

TIT is used with dosages based on age as follows:

Age (months)	Methotrexate (mg)	Hydrocortisone (mg)	Ara-C (mg)	Volume (ml)
<12	6	12	18	6
12-23	8	16	24	8
24-35	10	20	30	10
≥ 36	12	24	36	12

Frequency and total number of triple intrathecal treatments for Remission Induction is based on the patient's risk of CNS relapse, as follows:

1. All patients will receive triple intrathecal treatment at the disappearance of blast from PB, no later than D10. It is suggested to perform the 2nd TIT with bone marrow evaluation on D15.
2. Patients with any of the following features will receive totally 4 weekly TIT during induction therapy:
   - Philadelphia chromosome
   - *MLL* rearrangement

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

- Hypodiploidy (< 44)
- WBC >100,000/mm3 at presentation
- T-cell ALL
- t (1;19)/*E2A-PBX1*

3.Patients with any of the following features will receive TIT twice a week for 2 weeks followed by weekly TIT for 2 weeks (totally 6 TIT during induction therapy):

- CNS-2 status (<5 WBC/μL of CSF with blasts)
- CNS-3 status (≥ 5 WBC/ μ L of CSF with blasts or cranial nerve palsy)
- Traumatic lumbar puncture with blasts

Leucovorin rescue (5 mg/m^2/dose, max 5 mg) PO will be given at 24 and 30 hours after each triple intrathecal treatment during induction.

Follow plasma methotrexate levels (starting 24 hours after intrathecal therapy and until level becomes undetectable) in patients with renal dysfunction or extra fluid in third space, and rescue with leucovorin.

It is also important to correct hypertension and to prevent constipation during remission induction because patients with these features are at high risk of seizure (posterior reversible encephalopathy syndrome). Avoid syndrome of inappropriate antidiuretic hormone secretion from vincristine treatment.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

4.3 Consolidation Treatment (8 weeks)

When WBC >1500/mm^3, ANC >300/mm^3, platelet count >50,000/mm^3, and renal function is normal, consolidation treatment will be started.

Drug Dosages

VHR, HR	SR
MTX 5 gm/m^2 IV drip D1, 15, 29, 43	MTX 2.5 gm/m^2 IV drip D1, 15, 29, 43
6-MP 40 mg/m^2/day D1-56	6-MP 40 mg/m^2/day D1-56
TIT D1, 15, 29, 43 (8-12 hrs before HDMTX)	TIT D1, 15, 29, 43 (8-12 hrs before HDMTX)

The subsequent dose of HDMTX, 6-MP and IT will be delayed if WBC < 1,000/mm^3, ANC < 300/mm^3, platelet count < 50,000/mm^3, SGPT > 500U/L, total bilirubin > 2 mg/dl and direct bilirubin > 1.4 mg/dl, mucositis is present, or renal function is abnormal.

◎ Treatment Plans

Pre-hydration

At least two hours before high dose methotrexate, prehydration IV fluid (D5W + 40 mEq NaHCO3/L + 20 mEq KCl/L) will be administered at the rate of 200 ml/m^2/hr. At start of prehydration, one IV dose of NaHCO3 (unless otherwise clinically indicated, 12 mEq/m^2 for standard-risk patients and 25 mEq/m^2 for high-/very high-risk patients) diluted in 50 ml D5W will be given over 15 minutes. Prehydration fluid may also be given overnight at a rate of at least 100 ml/m^2/hr, especially in patients who had delayed clearance with prior course. High dose methotrexate treatment will follow, provided that urinary pH is >6.5; exceptions must be cleared with the pharmacokinetics service and the attending physician.

High Dose Methotrexate Infusion

Methotrexate loading dose will be given over 1 hour, followed immediately by maintenance infusion over 23 hours. During the methotrexate infusion, patients should receive hydration fluid with D5W + 40 mEq/L NaHCO3 + 20 mEq KCl/L at 100-150 ml/m^2/hr. Urine PH will be monitored with each void during infusion. An IV bolus of 12 mEq/m^2 NaHCO3 will be given if urine pH is 6.0; and 25 mEq/m^2 will be given if urine pH is <6.0. Acetazolamide 500 mg/m^2 orally every 6 to 8 hours may be used if systemic alkalosis limits the administration of bicarbonate for urinary alkalinization. Patients with evidence of renal dysfunction or delayed clearance during the methotrexate infusion may receive less than a 24 hour methotrexate infusion.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Leucovorin rescue

Leucovorin, 15 mg/m^2 (IV or PO) for high-/very high-risk or 10 mg/m^2 (PO or IV) for standard-risk cases, will be started at 42 hours after the start of methotrexate and repeated every 6 hours for a total of three doses. The dosage of leucovorin will be increased in patients with high plasma methotrexate concentrations (>1.0 μM at 42 hours) and continued until the methotrexate concentration is less than 0.10 μM. Additional measures, such as hydration, hemoperfusion, or carboxypeptidase will be considered in patients with 42-hour methotrexate levels > 10 μM. Patients with a history of delayed Grade 3 or 4 gastrointestinal toxicity with prior methotrexate or a history of typhlitis with any chemotherapy should have leucovorin continue for 5, rather than 3 doses; those with early toxicity should have leucovorin begin at 36 hours with subsequent methotrexate; if toxicity recurs, the baseline leucovorin dosage should also be increased.

Blood counts should be followed after high-dose methotrexate twice weekly; 6-MP dose should be reduced to half dose (20 mg/m^2/day) if WBC is between 1000 to 1500/mm^3, and should be held if WBC is less than 1000/mm^3.

Avoid the use of concomitant Bactrim or penicillin during high-dose methotrexate treatment because they will delay methotrexate clearance.

*Alternatively, monitoring of MTX levels (starting at 30 hrs) and leucovorin rescue regimen can follow the guidelines of TPOG-ALL-2002 Protocol. Please give adequate prehydration and bolus NaHCO3 before the infusion of high-dose MTX.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

4.4 REINTENSIFICATION TREATMENT (for Very High-Risk ALL)

Patients with very high-risk leukemia may receive reintensification therapy and then will be offered the option of transplant. This treatment will attempt to maximize leukemic cell kill before allogeneic hematopoietic stem cell transplantation (HSCT). For patients with Philadelphia chromosome positive ALL and positive MRD at the end of induction, ETP T-ALL, and those with induction failure or ≥1% leukemic lymphoblasts (determined by MRD study) in bone marrow at the end of remission induction (with the exception of hyperdiploid (51-68) and *TEL-AML1* cases who should have positive MRD after consolidation therapy), treatment will be given after consolidation therapy. However, consolidation therapy may be shortened, depending on patient's response to therapy and on the timing of transplantation.

For patients with ≥0.1% leukemic lymphoblasts (determined by MRD study) in bone marrow in week 7 of continuation treatment, this treatment will be given after the reinduction I. Upon marrow recovery (i.e., ANC≥300/mm^3, WBC≥1000/mm^3 and platelet count≥50,000/mm^3) after each course of reintensification, bone marrow examination with MRD study will be repeated.

兒癌- Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

This treatment course may be repeated only once if the patient still has persistently positive MRD (i.e. ≥ 0.01% blasts). Allogeneic hematopoietic stem cell transplantation may proceed after 1 course of the treatment if MRD becomes negative with the first course of treatment; otherwise, transplant will be performed after two courses of treatment. Patients deemed unsuitable for the transplant or who decline the procedure or whose donor has yet to be identified, will remain on study and receive subsequent chemotherapy as scheduled. The treatment scheme and dosage of chemotherapy are summarized below.

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	20 mg/m^2/day PO or IV (divided t.i.d)	18	Days 1-6
Cytarabine	2 grams/m^2, 3-hour IV infusion every 12 hours	4	Days 1-2
Etoposide	100 mg/m^2, 1-hour IV infusion every 12 hours	5	Days 3-5
TIT		1	Day 5
L-asparaginase	25,000iu/m^2 IM	1	Day 6

◎ Treatment Plans

Patients with suboptimal response to reintensification may receive one to two cycles of clofarabine/cyclophosphamide/etoposide/dexamethasone:

Agent	Dosage and Route	Doses	Schedule
Clofarabine	40 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m^2/day, 30-60 minute IV infusion	5	Days 1-5
Dexamethasone	8 mg/m^2/day (divided t.i.d)	15	Days 1-5

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

4.5 Continuation Treatment (120 weeks)

Post-remission continuation treatment begins after the completion of consolidation, provided that the ANC ≥300/mm^3, WBC ≥1500/mm^3 and platelet count ≥50,000/mm^3 as well as no evidence of mucositis. Continuation treatment (120 weeks) differs according to the risk classification, as follows (abbreviations as defined below).

Treatment (Weeks 1 to 20)

Week	VHR/HR	SR
1	DEX + EPI + VCR + 6MP + ASP§	6MP + DEX + VCR
2	6MP + ASP	6MP + MTX
3	#6MP + ASP	*6MP + MTX
4	DEX + EPI + VCR + 6MP + ASP	6MP + DEX + VCR
5	6MP + ASP	6MP + MTX
6	6MP + ASP	6MP + MTX
7	*†(Reind I)DEXx8d+VCR+EPI+ ASPx3	*(Reind)DEXx8d+VCR+EPI+ ASPx3
8	(Reind I) VCR+EPI+ASPx3	(Reind) VCR+ASPx3
9	(Reind I)DEXx7d+VCR+ASPx3	(Reind)DEXx7d+VCR+ASPx3
10	6MP + ASP	6MP + MTX
11	EPI + VCR + 6MP + ASP	6MP + MTX
12	*6MP + ASP	* 6MP + MTX
13	6MP + ASP	6MP + MTX
14	DEX + EPI + VCR + 6MP + ASP	6MP + DEX + VCR
15	6MP + ASP	6MP + MTX
16	6MP + ASP	6MP+ MTX
17	*†(Reind II)DEXx8d+VCR+ASPx3	*6MP + DEX + VCR
18	(Reind II) VCR+ ASPx3	6MP + MTX
19	(Reind II)DEXx7d+VCR+ASPx3	6MP + MTX
20	6MP + MTX	6MP + DEX + VCR

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

§ **First dose of ASP given at day 3 (after 2 days of DEX) to reduce the risk of ASP allergy**.

#Triple intrathecal treatment will be given to other standard/high-risk cases with WBC ≥100,000/mm^3, T-cell ALL, presence of Philadelphia chromosome, *MLL* rearrangement, t (1;19)/*E2A-PBX1*, hypodiploidy <44, or CNS-3 status, with CNS-2 or traumatic lumbar puncture with blasts at diagnosis..

*IT MHA (methotrexate + hydrocortisone + cytarabine)

† MRD study before each reinduction therapy will be done in patients with positive MRD at end of remission induction. Bone marrow sample will be used in B-lineage All and blood sample can be used for T-lineage ALL.

Patients with MRD ≥ 0.1% at week 7 receive reintensification treatment after Reinduction I

Dexamethasone, vincristine and L-asparaginase can be given regardless of blood counts, provided that the patient is not sick. Methotrexate, mercaptopurine and epirubicin will be held if ANC <300/mm^3, APC<500/mm^3, WBC <1,000/mm^3, or platelet count <50,000/mm^3.

(‡) Continue Dasatinib in cases with Ph, EBF1-PDGFRB or NUP214-ABL1

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Drug dosages, schedules and routes for continuation therapy weeks 1 to 6 and 10 to 16

DEX (dexamethasone)	12 mg/m^2(VHR/HR) or 8 mg/m^2 (SR) PO daily (tid) x 5 days, Days 1-5
EPI (epirubicin)	30 mg/m^2 IV, Day 1
VCR (vincristine)	2.0 mg/m^2 IV push (max. 2 mg), Day 1 (0.05 mg/kg for patients < 1 year of age or < 10kg in weight)
6MP (6-mercaptopurine)	40 mg/m^2 PO h.s.daily x 7 days (VHR/ HR), Days 1-7 50 mg/m^2 PO h.s. daily x 7 days (SR), Days 1-7
ASP (L-asparaginase)	10,000 U/m^2 IM, Day 1
MTX (methotrexate)	40 mg/m^2 IV or IM, Day 1

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

REINDUCTION TREATMENT

This phase of treatment will be started at weeks 7 and/or 17 if patients have ANC ≥500/mm^3, WBC ≥1500/mm^3, and platelet count ≥50,000/mm^3.

Intrathecal treatment will be followed by leucovorin rescue (5 mg/m^2/dose PO, max 5 mg) at 24 and 30 hours **only in patients with prior CNS toxicities or in patients with WBC < 1500/mm3, or ANC < 500/mm^3**

Reinduction I for VHR/HR ALL excluding infant with *MLL*+(3 weeks)

Agents	Dosages and routes	#Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
Epirubicin	30 mg/m^2	2	Days 1,8
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3,5,7,10,12,14, 17,19,21
Methotrexate+ hydrocortisone + Ara-C	Age-dependent, IT	1	Day 1

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Reinduction II for VHR/HR ALL including infant with *MLL*+ (3 weeks)

Agents	Dosages and routes	#Doses	Schedules
Dexamethasone	12 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2/thrice weekly IM	9	Days 3, 5, 7, 10,12, 14,17,19,21
Methotrexate+ hydrocortisone + Ara-C	Age-dependent, IT	1	Day 1

Reinduction for SR ALL (3 weeks)

Agents	Dosages and routes	Doses	Schedules
Dexamethasone	10 mg/m^2/day PO (t.i.d.)	45	Days 1-8, 15-21
Vincristine	1.5 mg/m^2/week IV (max 2 mg)	3	Days 1, 8, 15
L-asparaginase	6,000 U/m^2 thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14,17,19,21
Epirubicin	30 mg/m^2/week IV	1	Day 1
Methotrexate+ hydrocortisone + Ara-C	Age-dependent, IT	1	Day 1

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Reinduction I for infant with *MLL+*

Agent	Dosage and Route	Doses	Schedule
Dexamethasone	8 mg/m^2/day (divided t.i.d)	45	Days 1-8; Days 15-21
Clofarabine	40 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Etoposide	100 mg/m^2/day, 2-hour IV infusion	5	Days 1-5
Cyclophosphamide	300 mg/m^2/day, 1-hour IV infusion	5	Days 1-5
L-asparaginase	6,000 U/m^2 thrice weekly IM	9	Days 3, 5, 7, 10, 12, 14, 17, 19, 21
Methotrexate+ hydrocortisone + Ara-C	Age-dependent, IT	1	Day 1

For infants < 1 month of age, or for infants < 3 months of age born significantly prematurely, a 50% reduction in dosages of asparaginase, etoposide, cyclophosphamide, epirubicin, and clofarabine should be made.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　　2018年第一版

◎ Treatment Plans

Treatment (weeks 21 to end of therapy)

Week	HR	SR
21	6MP + MTX	6MP + MTX
22	6MP + MTX	6MP + MTX
23	Cyclo + Ara-C	6MP + MTX
24	*DEX + VCR	*6MP + DEX + VCR
25	6MP + MTX	6MP + MTX
26	6MP + MTX	6MP + MTX
27	Cyclo + Ara-C	6MP + MTX
28	*DEX + VCR	*)6MP + DEX + VCR

*TIT

(*)IT MHA for standard-risk cases, *TEL-AML*1 fusion and hyperdiploidy (51-68) with WBC > 100,000/mm^3 , CNS-2 or traumatic lumbar puncture with blast.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Drug Dosages, Schedules and Routes for Continuation Therapy from Week 21 to End of Therapy

6MP (6-mercaptopurine)	60 mg/m^2 PO h.s. daily x 7 days, Days 1-7
MTX (methotrexate)	40 mg/m^2 IV or IM(or PO, if parenteral route is not feasible), Day 1
Cyclo (Cyclophosphamide)	300 mg/m^2 IV, Day 1 (VHR/HR)
Ara-C (Cytarabine)	300 mg/m^2 IV, Day 1 (VHR/HR)
DEX (dexamethasone)	12 mg/m^2 (VHR/HR) or 8 mg/m^2 (SR) PO daily (tid) x 5, Day 1-5
VCR (vincristine)	2.0 mg/m^2 IV push (max. 2 mg), Day 1

The same treatment (weeks 21-28) will be repeated for a total of 6 times (until week 68). After week 68, cyclophosphamide and cytarabine will be replaced by daily 6MP and methotrexate; all patients will then receive daily 6MP and weekly MTX with pulses of dexamethasone and vincristine every 4 weeks until week 100, after which only 6MP and methotrexate will be given.

Cyclophosphamide and cytarabine dosages may need to be reduced by 33% to 50% in patients who repeatedly have very low counts (WBC < 1000/mm^3 or ANC < 300/mm^3 or platelets < 50,000/mm^3) one to two weeks later.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Treatment Plans

Dexamethasone dose decreases to 6 mg/m^2 beginning week 68.

Continuation therapy will be discontinued after 120 weeks.

4.6 IT Chemotherapy During Continuation Treatment

-Triple intrathecal treatment will be given to SR cases with CNS-1 status (no identifiable blasts in CSF) on weeks 3, 7, 12, 17, 24, 32, 40, and 48. (14 times)

-Triple intrathecal treatment will be given to SR cases with CNS-2 or traumatic CSF with blasts status on weeks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48. (19 times)

-Triple intrathecal treatment will be given to HR cases with CNS-1 status on weeks 7, 12, 17, 24, 28, 32, 36, 40, 44 and 48. (16 Times)

-Triple intrathecal treatment will be given to other high/very high-risk cases with WBC ≥ 100,000/mm^3 at presentation, , T-cell ALL, t (1;19)/*E2A-PBX1*,presence of Philadelphia chromosome, *MLL* rearrangement, hypodiploidy <44, CNS-2 or CNS-3 status, or traumatic lumbar puncture with blasts on weeks 3, 7, 12, 17, 24, 28, 32, 36, 40, 44, 48, 56, 64, 72, 80, 88 and 96. (25 Times)

◎ Treatment Plans

Leucovorin will not be given after intrathecal treatment during continuation treatment unless the patient has an adverse reaction with previous intrathecal or methotrexate treatment, e.g., seizure or encephalopathy, has renal dysfunction resulting in high plasma methotrexate concentration, or has Down syndrome. Leucovorin may be given when patient is neutropenic, at treating physician's discretion; however, it is generally preferable to delay intrathecal therapy if patient has neutropenia. Down syndrome patients will receive leucovorin with every LPIT.

Note that WBC and ANC counts should be double a week following dexamethasone pulse therapy. If WBC or ANC counts fail to double (indicating low bone marrow reserve), 6-MP and MTX dosages should be reduced to half. If WBC or ANC remains the same or is lower, 6-MP and MTX should be held because the patient is at high risk of infection, and blood counts should be repeated in 3 to 4 days to decide if 6-MP can be resumed. Patients 10 years of age or old are at especially high risk of sepsis. If patient has abdominal pain, typhlitis must be excluded and antibiotics may be started even if the patient has no fever.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Patient evaluation

Pretreatment Evaluation

1. Complete history and physical exam with careful notation and assessment of clinical signs relevant to leukemia: liver, spleen, lymph nodes, gum or skin infiltration, local or systemic infections, testes
2. Complete blood count, differential and platelet count
3. Chemical profile: glucose, BUN, creatinine, LDH, uric acid, Alk-P, bilirubin, SGOT, SGPT, calcium, phosphorous, sodium, potassium, total protein, and albumin
4. Hepatitis B surface antigen
5. Lumbar puncture with CSF routine examination and cytospin
6. Bone marrow evaluation for cytomorphology and cytochemistries, surface markers, cytogenetics, DNA index and molecular assay (if available)
7. Chest X-Ray (PA and/or lateral)
8. Blood culture for all febrile patients
9. Other clinical investigations including echocardiogram, computed tomography, sinus films, etc., if clinically indicated

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Patient evaluation

Post-treatment Evaluation

1. Postprandial blood sugar, albumin, amylase, lipase BiW during L-asparaginase therapy
2. Sodium QW in induction therapy (watching for SIADH)
3. Chemical profile, if needed, esp. within 48 hours after chemotherapy is started.
4. BUN and creatine before and after HDMTX
5. CBC
6. Plasma MTX level after HDMTX therapy

Evaluation Criteria

1. Complete remission: M1 marrow status with restoration of normal hematopoiesis and normal performance status. These findings must persist for a least one month.
2. Induction failure: ≥ 5% leukemic blasts in marrow after 42 days of remission induction treatment.
3. Bone marrow relapse: ≥ 25% leukemic blasts in marrow
4. CNS relapse: ≥ 5 WBC/μL of CSF with definite blasts on cytospin preparation
5. Testicular relapse: Isolated testicular relapse must be confirmed pathologically; in the event of bone marrow relapse, combined testicular relapse can be based on testicular enlargement (documented by sonogram) without biopsy.

兒癌- Leukemia ALL

高雄榮民總醫院
臨床診療指引　　2018年第一版

◎ Patient evaluation

Patient Exclusions

Except for the patients who are entered but subsequently found not to have met the eligibility criteria, all patients will be included in all analyses. Thus, if a patient achieves remission but is subsequently removed from the study because of toxicity, the outcome (time to failure, survival, ect.) for that patient is included in analysis. Patients removal from study because of refusal of therapy could be censored at the time.

Primary End-Points (definitions)

There are eight primary end-points that are commonly used in the analysis of leukemia studies. These are listed and defined below. Seven of the eight end-points measure the time from some starting point to the time of "failure" so that methods for handling censored data must be used. (A censored observation occurs when a patient has not yet failed.)

Complete Remission (CR) – This is a "yes-no" variable that refers to a complete remission attained on the specified induction regimen. If a patient is taken off study prior to attaining a CR, then that patient is counted as a non-responder, even if a CR was achieved later on a different therapy.

◎ Patient evaluation

hematologic relapse has occurred, this is the same as the hematologic remission duration and the event is censored at the time of hematologic relapsed. Other relapses (e.g., testicular) are also counted as censored observations.

Time to Testicular Relapse – Time from the initial CR date to the date of testicular relapse, or the last follow-up date for boys who have not had a testicular relapse. A death or second malignancy prior to a testicular relapse is counted as a censored observation with respect to time to testicular relapse. Non-testicular relapses (hematologic or other) are not counted as failures and are ignored for the analysis of time to testicular relapse.

◎ CONTINGENCY PLANS FOR REFRACTORY DISEASE OR RELAPSE

Induction failures

Patients who do not attain complete remission (≥ 5% leukemic blasts in bone marrow) after remission induction, consolidation treatment and reintensification treatment will be removed from the protocol. Those who do not achieve a remission after induction therapy, but subsequently attain complete remission after consolidation or reintensification treatment, are candidates for allogeneic hematopoietic stem cell transplantation.

Hematologic relapse

Patients with ≥ 25% lymphoblasts in marrow aspirate will become eligible for relapse protocols.

Extramedullary relapse

Patients with any form of extramedullary relapse (testes, ovarian, etc) except that of CNS will become eligible for relapse protocols. Patients with overt CNS relapse (i.e. ≥ 5 WBC/μL of CSF with blasts) will remain on study and receive treatment outlined in Section 9.4. Patients who have <5 WBC/μL of CSF with identifiable blasts are not considered to have overt CNS relapse and will be treated as outlined in Section 9.4.

◎ CONTINGENCY PLANS FOR REFRACTORY DISEASE OR RELAPSE

Those patients receiving cranial irradiation only should receive 4 to 5 triple intrathecal therapy with leucovorin rescue during irradiation. No TIT will be given after cranial irradiation.

Mercaptopurine and methotrexate will be withheld for at least one week prior to and during irradiation.

Systemic chemotherapy during irradiation will include dexamethasone and vincristine with or without L-asparaginase.

Continuation treatment will be given for at least one year from time of relapse (or at least 2½ years from the start of treatment).

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Supportive care

Fever at Diagnosis

All patients with fever at diagnosis will be admitted for broad spectrum parenteral antibiotic treatment until an infectious etiology can be excluded.

Metabolic Derangements

It is important to prevent or treat hyperuricemia and hyperphosphatemia with secondary hypocalcemia resulting from spontaneous or chemotherapy-induced leukemic cell lysis, especially in T-cell ALL.

Patients with large leukemic cell burden should receive hydration and oral phosphate binder.

Patients with large leukemic cell burden with or without hyperuricemia (e.g., WBC ≥ 100,000/mm^3, uric acid ≥ 7.5 mg/dl or ≥ 6.5 mg/dl in patients <13 years old) may be treated with rasburicase if they have no history of G6PD deficiency or ongoing pregnancy. Patients with history of severe allergy (e.g., bronchial asthma requiring bronchodilator, atopic eczema), may be enrolled on RASALL. For all other patients not at high risk of hyperuricemia, hydration, allopurinol, and judicious use of alkalinization (keeping urine pH between 6.5 and 7.4) may be sufficient.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Supportive care

Hyperleukocytosis

For patients with extreme hyperleukocytosis (i.e., WBC ≥ 300,000/mm^3), leukapheresis or exchange transfusion (in small children) may be considered. The Director of the Blood Bank should be consulted for this procedure.

Avascular Necrosis of Bone

Osteonecrosis of the bone, a known complication of treatment with corticosteroids, can be expected to occur in approximately 10-15% of patients, especially in those older than nine years of age. This devastating complication may result in collapse of the articulating surface with subsequent pain and development of arthritis. Early detection of small lesions will permit intervention which may prevent pain and irreversible damage of the joints. In this study, all patients 9 years of age and older will have MRI scans of the pelvis/hips and knees after each reinduction phase, at off therapy date, and as needed thereafter. Patients diagnosed with osteonecrosis will be referred to orthopedics. Any patient who develops symptoms of joint pain prior to or between scheduled MRI scans should have an MRI performed to rule out osteonecrosis or progression of this complication.

◎ Supportive care

For patients who require surgical intervention, treatment will vary based on degree of progression, i.e., observation, core decompression, bone grafting and resurfacing hemiarthroplasty.

Pancytopenias

Patients with prolonged (> 3 weeks) unexplained anemia (hemoglobin < 7 g/dl) or neutropenia (ANC < 300/mm^3) during remission should be evaluated for B19 parvovirus infection or hemolysis or toxicity from non-chemotherapeutic agents (e.g., TMP/SMZ).

Nutritional Supplementation

Nutritional or vitamin therapies should not result in patients receiving more than the RDA for folic acid with dietary and supplement intake, to prevent interference with the effectiveness of methotrexate.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Supportive care

Drug Interactions

Because concurrent use of enzyme inducing anticonvulsants (e.g. phenytoin, phenobarbital, and carbamazepine) with antileukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes. Gabapentin does not induce hepatic drug metabolizing enzymes and may be a suitable alternative anticonvulsant.

Azole antifungals (fluconazole, itraconazole, and ketoconazole) and the macrolide antibiotics (erythromycin, rifampin, and zithromax) may have potent inhibitory effects on drug-metabolizing enzymes, and the doses of some antileukemic drugs (e.g. vincristine, anthracyclines, etoposide) may need to be reduced in some patients on chronic treatments.

Penicillins interfere with tubular excretion of methotrexate, and it is recommended that an alternative non-penicillin antibiotic be used.

◎ Supportive care

Down Syndrome

Patients with Down's syndrome should be closely monitored for toxicity, and offered aggressive supportive care. Methotrexate dosage will be reduced as described in section 6. Historically, most of these patients will be treated in the low-risk category, and should have their chemotherapy doses appropriately reduced to avoid undue toxicity. Oral leucovorin (5 mg/ m^2 q 12 hr x 2) should be given 24 hrs after each IT MHA. A 30% dose reduction of dexamethasone and/or high dose cytarabine should be considered for Down's syndrome patients treated on the high-risk /very high-risk arm who experience higher than expected toxicity during earlier phases of therapy.

兒癌– Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Supportive care

RSV prophylaxis

All infants should receive RSV prophylaxis as per current institutional policy.

Prophylactic antibiotics during periods of prolonged neutropenia

Patients with expected periods of severe neutropenia (ANC<500) of 7 days or longer (e.g. during induction, reinduction, and intensification) should receive prophylactic antibiotics (ciprofloxacin 250-350 mg/m^2/12h plus vancomycin 400 mg/m^2/12h) and antifungals (micafungin, 1 mg/kg/day with max. 50mg/day, if patient is receiving weekly vincristine, or voriconazole 4mg/kg/12h if patient has completed all vincristine doses in the treatment phase).

兒癌- Leukemia ALL

高雄榮民總醫院
臨床診療指引　2018年第一版

◎ Toxicity and complications criteria

Toxicity of chemotherapy will be evaluated using the ECOG guidelines (see Appendix I of TPOG ALL-93 protocol)

Definitions of infection (see Appendix II of TPOG ALL-93 protocol)

◎Drop off criteria

1.Incorrect diagnosis.
2.Patient and/or parents refuse to allow additional therapy.
3.A patient who, in the judgement of the Principal Investigator, could not or did not follow the assigned treatment, may be removed from study.
4.Patients who fail to meet all eligibility requirements of protocol (i.e., ineligible) will be taken off study, e.g., using other protocols, or not newly diagnosed patients.

◎癌症藥物停藥準則

骨髓及血液檢查，腫瘤有復發或變大情況，應停止或改變治療方式。

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